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# Percutaneous Coronary Intervention in Patients Receiving Enoxaparin or Unfractionated Heparin After Fibrinolytic Therapy for ST-Segment Elevation Myocardial Infarction in the ExTRACT-TIMI 25 Trial

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**Objectives** We sought to evaluate whether enoxaparin (ENOX) is superior to unfractionated heparin (UFH) as adjunctive therapy for patients with ST-segment elevation myocardial infarction (STEMI) who receive fibrinolytic therapy and subsequently undergo percutaneous coronary intervention (PCI) by analyzing data from the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) trial.

**Background** Limited data are available on the use of ENOX compared with UFH as adjunctive therapy in STEMI patients treated with fibrinolytic therapy and subsequent PCI.

**Methods** A total of 20,479 STEMI patients who received fibrinolytic therapy were randomized to a strategy of ENOX throughout index hospitalization or UFH for at least 48 h, with blinded study drug to continue if PCI was performed. The primary end point of death or recurrent MI through 30 days was compared for ENOX versus UFH among the patients who underwent subsequent PCI ($n = 4,676$).

**Results** After initial fibrinolysis, fewer patients underwent PCI through 30 days in the ENOX versus the UFH group (22.8% vs. 24.2%; $p = 0.027$). Among patients who underwent PCI by 30 days, the primary end point occurred in 10.7% of ENOX and 13.8% of UFH patients (0.77 relative risk; $p < 0.001$). There were no differences in major bleeding for ENOX versus UFH (1.4% vs. 1.6%; $p =$ NS). Results were similar when PCI was carried out in patients receiving blinded study drug during PCI ($n = 2,178$).

**Conclusion** Among patients treated with fibrinolytic therapy for STEMI who underwent subsequent PCI, ENOX administration was associated with a reduced risk of death or recurrent MI without difference in the risk of major bleeding. The strategy of ENOX support for fibrinolytic therapy followed by PCI is superior to UFH and provides a seamless transition from the medical management to the interventional management phase of STEMI without the need for introducing a second anticoagulant in the cardiac catheterization laboratory. (J Am Coll Cardiol 2007;49: 2238–46) © 2007 by the American College of Cardiology Foundation

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Compared with primary percutaneous coronary intervention (PCI), fibrinolytic therapy for ST-segment elevation myocardial infarction (STEMI) is limited by recurrent MI, bleeding, and the risk of intracranial hemorrhage (1). One approach to limit the risk of reinfarction following fibrinolytic agent administration is the performance of PCI,

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but data supporting this approach are conflicting (2–5). Older studies indicated that PCI after fibrinolytic agent administra-

tion was associated with an increased risk of adverse outcomes (2–5). However, newer adjunctive pharmacotherapies and improved interventional devices may reduce the hazard associated with PCI after fibrinolytic agent administration (6), and contemporary trial databases offer the opportunity to re-evaluate the approach of performing PCI in patients who previously received a fibrinolytic.

The ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) trial compared a strategy of enoxaparin (ENOX) with unfractionated heparin (UFH) as adjunctive therapy for fibrinolysis among STEMI patients (7,8). The present prospectively planned analysis of the ExTRACT-TIMI 25 trial evaluated the hypothesis that a strategy of ENOX for the duration of the index hospitalization is superior to UFH as adjunctive therapy for fibrinolytic therapy among patients who subsequently undergo PCI.

**Abbreviations and Acronyms**

**ENOX** = enoxaparin
**PCI** = percutaneous coronary intervention
**STEMI** = ST-segment elevation myocardial infarction
**UFH** = unfractionated heparin

## Methods

**Patient population.** The STEMI patients treated with fibrinolytic agents were randomized in 48 countries (7,8). Eligible patients were at least 18 years of age, had at least 20 min of ischemic symptoms while at rest within 6 h before randomization, had ST-segment elevation of at least 0.1 mV in 2 limb leads or of 0.2 mV in at least 2 contiguous precordial leads or left bundle-branch block, and were scheduled to undergo fibrinolysis.

**Study protocol.** After treatment with a fibrinolytic agent and aspirin, patients were randomized to either ENOX or UFH in a double-blind double-dummy design to continue until hospital discharge or a maximum of 8 days (whichever came first) as previously described (7).

Patients undergoing PCI were to receive antithrombotic support with blinded study drug. Before PCI, a blinded dose of 0.3 mg/kg of ENOX (or matched placebo) was administered intravenously if the last subcutaneous dose was 8 to 12 h earlier, whereas no additional ENOX (or matched placebo) was administered if the last subcutaneous dose was administered within the preceding 8 h. Unfractionated heparin (or matched placebo) was dosed according to the activated clotting time, using a target of 200 s for patients receiving and 250 s for those not receiving a glycoprotein IIb/IIIa inhibitor. The activated clotting time was encrypted so as not to break the blinding. All monitoring of anticoagulation to adjust the dose of UFH to maintain an

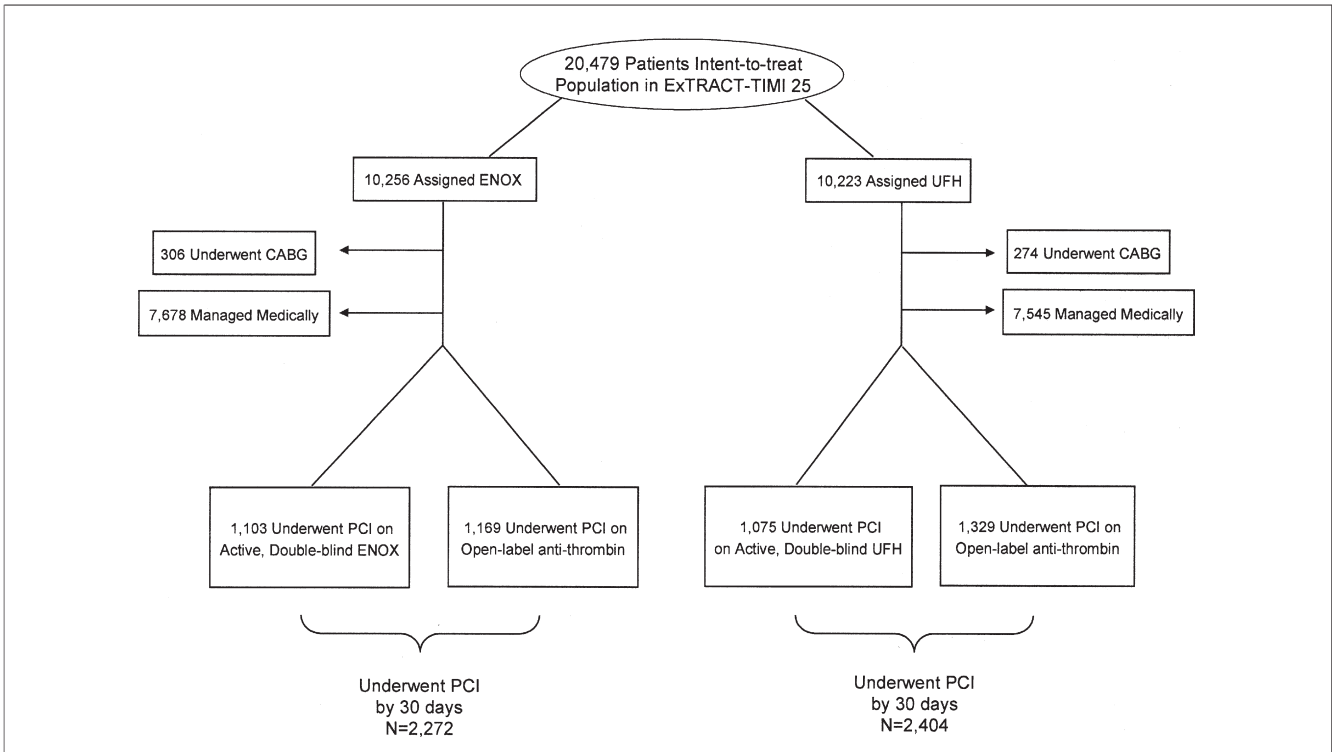


**Figure 1** Study Profile

Number of patients in the enoxaparin (ENOX) and unfractionated heparin (UFH) groups treated with coronary artery bypass graft (CABG), medical therapy, and percutaneous coronary intervention (PCI).

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activated partial thromboplastin time of 1.5 to 2.0 times the control value was performed in a blinded fashion by personnel caring for the patient or in an unblinded fashion by a designated medical professional not involved in the patient's care. If a closure device was used, the sheath was to be removed at the end of the PCI; however, if no closure device was used, the sheath was to be removed at least 6 h after the last intravenous or subcutaneous dose of blinded study drug. The blinded study medication was not to be restarted after uncomplicated PCI procedures but was to be restarted after groin hemostasis was achieved in patients in whom antithrombotic therapy was considered necessary clinically.

Although PCI could be performed at any time for failed fibrinolysis or in response to an episode of recurrent MI/ischemia, the protocol recommended that elective procedures be deferred for at least 48 h after randomization. For PCI performed after day 8 or hospital discharge, open-label UFH was to be used irrespective of the original treatment assignment. Clopidogrel was administered at the investigator's discretion. Patients were followed for clinical end points and adverse events during the index hospitalization and at day 30 (range day 31 to day 38) in person or by telephone.

**End points.** The prespecified primary efficacy end point of the trial and of this substudy was the composite of all-cause mortality or nonfatal recurrent MI through 30 days (7). The additional secondary end point of net clinical benefit was the composite of death or recurrent nonfatal MI or nonfatal TIMI major bleed. All ischemic and clinically significant bleeding events were adjudicated by a blinded independent clinical events committee using prespecified definitions (7,8).

The main analysis included patients who underwent PCI by 30 days. An additional analysis was conducted in patients who underwent PCI while receiving double-blind study drug.

**Statistical analysis.** All efficacy and net clinical benefit comparisons were analyzed by the intention-to-treat principle. All safety analyses were performed according to the

**Table 1 Baseline Characteristics by Performance of PCI by 30 Days**

| | PCI (n = 4,676) | No PCI (n = 15,223) | p Value |
|---|---|---|---|
| Baseline characteristics | | | |
| Age, yrs | 57 (50, 66) | 60 (51, 70) | <0.001 |
| Age ≥75 yrs, n (%) | 339 (7.3) | 2,154 (14.2) | <0.001 |
| Male gender, n (%) | 3,856 (82.5) | 11,332 (74.4) | <0.001 |
| White race, n (%) | 3,801/4,676 (81.3) | 13,584/15,222 (89.2) | <0.001 |
| Weight, kg | 76 (69, 85.1) | 76 (68, 85) | 0.03 |
| Hypertension, n (%) | 1,733/4,631 (37.4) | 6,935/15,027 (46.2) | <0.001 |
| Hyperlipidemia, n (%) | 965/4,257 (22.7) | 1,808/11,195 (16.2) | <0.001 |
| Current smoker, n (%) | 2,388/4,675 (51.1) | 7,068/15,214 (46.5) | <0.001 |
| Diabetes mellitus, n (%) | 755/4,639 (16.3) | 2,176/15,037 (14.5) | 0.003 |
| Prior MI, n (%) | 514/4,660 (11.0) | 2,066/15,168 (13.6) | <0.001 |
| Prior angina pectoris, n (%) | 992/4,648 (21.3) | 4,551/15,122 (30.1) | <0.001 |
| Prior PCI, n (%) | 290/4,668 (6.2) | 344/15,215 (2.3) | <0.001 |
| Index presentation and medications | | | |
| Anterior MI, n (%) | 1,889/4,659 (40.6) | 6,792/15,098 (45.0) | <0.001 |
| Chronic treatment with aspirin, n (%) | 730/4,666 (15.7) | 1,908/15,192 (12.6) | <0.001 |
| UFH within 3 h before randomization, n (%) | 931/4,676 (19.9) | 2,172/15,222 (14.3) | <0.001 |
| LMWH within 7 days before randomization, n (%) | 31 (0.7) | 58 (0.4) | 0.01 |
| Creatinine clearance, ml/min | 87.1 (69.2, 107.9) | 80.6 (61.7, 103.4) | <0.001 |
| Killip classification ≥II, n (%) | 393/4,669 (8.4) | 1,854/15,219 (12.2) | <0.001 |
| TIMI risk score >3, n (%) | 1,247/4,595 (27.1) | 5,789/15,109 (38.3) | <0.001 |
| Time from symptom onset to start of fibrinolytic therapy, h | 2.7 (1.8, 3.9) | 3.3 (2.3, 4.3) | <0.001 |
| Fibrinolytic agent | | | <0.001 |
| Fibrin-specific, n (%) | 3,678 (78.6) | 12,143 (79.7) | |
| Streptokinase, n (%) | 976 (20.9) | 3,047 (20.0) | |
| Cardiac medications during index hospitalization | | | |
| Aspirin, n (%) | 4,563 (97.6) | 14,353 (94.3) | <0.001 |
| Clopidogrel, n (%) | 3,160 (67.6) | 2,356 (15.5) | <0.001 |
| Beta-blockers, n (%) | 4,028 (86.1) | 13,020 (85.5) | 0.30 |
| ACE inhibitors or angiotensin-receptor blockers, n (%) | 3,744 (80.1) | 12,111 (79.6) | 0.45 |
| Statin, n (%) | 3,987 (85.3) | 9,734 (63.9) | <0.001 |
| GP IIb/IIIa inhibitors, n (%) | 811 (17.3) | 55 (0.4) | <0.001 |

Continuous variables are shown as median (interquartile range).

ACE = angiotensin-converting enzyme; GP = glycoprotein; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

**Table 2 Propensity to Undergo PCI by 30 Days***

| | Odds Ratio (95% CI) | p Value |
|---|---|---|
| Age (10 yrs) | 0.81 (0.78–0.84) | <0.001 |
| SBP (10 mm Hg) | 1.03 (1.01–1.05) | 0.003 |
| Heart rate (10 beats/min) | 0.93 (0.91–0.95) | <0.001 |
| Time from symptom onset to fibrinolytic (h) | 0.93 (0.90–0.95) | <0.001 |
| Gender (male) | 1.20 (1.08–1.33) | <0.001 |
| History of hypertension | 1.15 (1.06–1.26) | 0.001 |
| Prior MI | 0.85 (0.73–0.98) | 0.030 |
| Prior PCI | 1.47 (1.20–1.81) | <0.001 |
| Prior aspirin use | 1.13 (1.01–1.26) | 0.042 |
| Anterior MI | 1.08 (1.00–1.17) | 0.053 |
| Randomized to ENOX compared with UFH | 0.91 (0.84–0.98) | 0.011 |

*Model also includes individual countries, which are not shown owing to space constraints.
CI = confidence interval; ENOX = enoxaparin; SBP = systolic blood pressure; other abbreviations as in Table 1.

treatment actually received by the patient. For patients who underwent more than 1 PCI, the first procedure was counted as the index procedure in the analysis. Patients who underwent coronary artery bypass grafting were excluded from the analysis. In the comparison of baseline characteristics, differences in continuous variables were analyzed using the Wilcoxon rank sum test, and differences in categoric variables were analyzed using the chi-square test. Clinical event data are reported as percentages and relative risk comparing ENOX and UFH. For the primary end point, multivariate analysis was performed using a logistic regression model (results displayed as adjusted [$OR_{adj}$]) that included terms for treatment group, age, earlier aspirin use, smoking, time from symptom onset to fibrinolytic agent, type of fibrinolytic agent used (fibrin-specific or streptokinase), duration of antithrombin therapy before PCI, and the propensity to undergo PCI. The propensity score was constructed by applying a forward selection algorithm with an inclusion p value threshold of <0.05 to a logistic regression model predicting PCI in the entire trial cohort and containing candidate baseline variables that included demographics, traditional cardiovascular risk factors, earlier

**Table 3 Baseline Characteristics by Treatment Group Among Patients Undergoing PCI by 30 Days**

| | ENOX (n = 2,272) | UFH (n = 2,404) | p Value |
|---|---|---|---|
| Baseline characteristics | | | |
| Age, yrs | 57 (50, 66) | 57 (49, 66) | 0.45 |
| Age ≥75 yrs, n (%) | 164 (7.2) | 175 (7.3) | 0.94 |
| Male gender, n (%) | 1,867 (82.2) | 1,989 (82.7) | 0.61 |
| White race, n (%) | 1,843 (81.2) | 1,958 (81.5) | 0.78 |
| Weight, kg | 76 (69, 86) | 77 (69, 85) | 0.44 |
| Hypertension, n (%) | 869/2,249 (38.6) | 864/2,382 (36.3) | 0.10 |
| Hyperlipidemia, n (%) | 454/2,062 (22.0) | 511/2,195 (23.3) | 0.33 |
| Current smoker, n (%) | 1,171/2,272 (51.5) | 1,217/2,403 (50.7) | 0.54 |
| Diabetes mellitus, n (%) | 368/2,254 (16.3) | 387/2,385 (16.2) | 0.93 |
| Prior MI, n (%) | 246/2,266 (10.9) | 268/2,394 (11.2) | 0.71 |
| Prior angina pectoris, n (%) | 481/2,257 (21.3) | 511/2,391 (21.4) | 0.96 |
| Prior PCI, n (%) | 147/2,267 (6.5) | 143/2,401 (6.0) | 0.46 |
| Index presentation and medications | | | |
| Anterior MI, n (%) | 925/2,263 (40.9) | 964/2,396 (40.2) | 0.66 |
| Chronic treatment with aspirin, n (%) | 369/2,266 (16.3) | 361/2,400 (15.0) | 0.24 |
| UFH within 3 h before randomization, n (%) | 471 (20.7) | 460 (19.1) | 0.17 |
| LMWH within 7 days before randomization, n (%) | 12 (0.5) | 19 (0.8) | 0.27 |
| Creatinine clearance, ml/min | 86.3 (69.1, 107.5) | 88.14 (69.3, 108.2) | 0.43 |
| Killip classification ≥II, n (%) | 180/2,266 (7.9) | 213/2,403 (8.9) | 0.26 |
| TIMI risk score >3, n (%) | 615/2,222 (27.7) | 632/2,373 (26.6) | 0.43 |
| Time from symptom onset to start of fibrinolytic therapy, h | 2.7 (1.8, 4.0) | 2.8 (1.8, 3.9) | 0.77 |
| Fibrinolytic agent | | | 0.81 |
| Fibrin-specific, n (%) | 1,779 (78.3) | 1,899 (79.0) | |
| Streptokinase, n (%) | 480 (21.1) | 496 (20.6) | |
| Cardiac medications during index hospitalization | | | |
| Aspirin, n (%) | 2,207 (97.1) | 2,356 (98.0) | 0.05 |
| Clopidogrel, n (%) | 1,504 (66.2) | 1,656 (68.9) | 0.05 |
| Beta-blockers, n (%) | 1,957 (86.1) | 2,071 (86.2) | 0.99 |
| ACE inhibitors or angiotensin-receptor blockers, n (%) | 1,832 (80.6) | 1,912 (79.5) | 0.35 |
| Statin, n (%) | 1,924 (84.7) | 2,063 (85.8) | 0.28 |
| GP IIb/IIIa inhibitors, n (%) | 350 (15.4) | 461 (19.2) | 0.001 |
| PCI performed on blinded study drug, n (%) | 1,103 (11.3) | 1,075 (11.0) | 0.53 |

Continuous variables are shown as median (interquartile range).
Abbreviations as in Tables 1 and 2.

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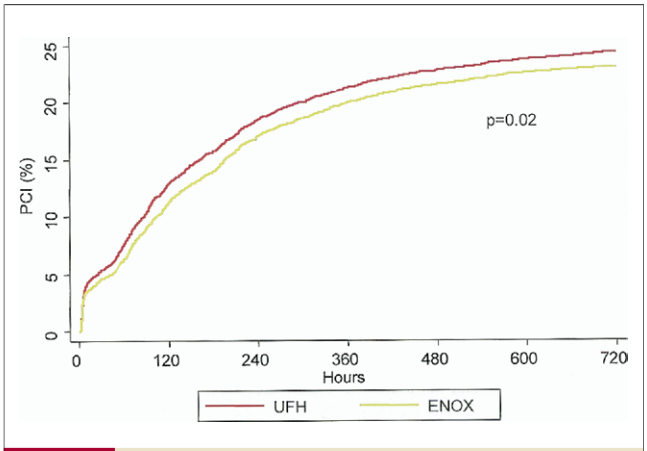


**Figure 2** **Kaplan-Meier Failure Estimates for PCI by Randomization Group**

PCI was performed less frequently in the ENOX group than in the UFH group (p = 0.02 by log rank). Abbreviations as in Figure 1.

cardiac disease and procedures, time to presentation, initial vital signs, infarct location, type of fibrinolytic agent, and treatment allocation.

All statistical analyses were performed using Stata/SE, version 9.0 (Stata Corp., College Station, Texas).

## Results

A total of 4,676 (23%) of the 20,479 patients in the intention to treat cohort in the ExTRACT–TIMI 25 trial underwent PCI by 30 days and represent the main cohort for the present analysis (Fig. 1). There were significant differences in the baseline characteristics of those patients who did and did not undergo PCI (Table 1), and a propensity score was developed to adjust for these differences (Table 2). This propensity score for performance of PCI included terms for age, earlier MI, earlier PCI, systolic blood pressure and heart rate at presentation, earlier aspirin use, history of hypertension, gender, anterior MI, time from symptom onset to administration of fibrinolytic agent, and randomized treatment group and country (Table 2). The c-statistic for the propensity for performance of PCI model was 0.82.

Among those patients treated with PCI, the 2 treatment groups (ENOX vs. UFH) were similar with regard to baseline characteristics (Table 3). The PCI was performed on blinded study drug in 1,103 of 2,110 patients in the ENOX group (52.3%) and 1,075 of 2,238 patients in the UFH group (48.0%; p = 0.005).

**Efficacy end points. INCIDENCE AND RELATIVE TIMING OF URGENT AND NONURGENT PCI.** Enoxaparin was associated with a reduction in the frequency of PCI (22.8% vs. 24.2%; p = 0.027) as well as a 12-h median delay in the timing of performance of PCI (121.7 h vs. 109.2 h; p = 0.006) (Fig. 2). Among patients who did not sustain recurrent ischemia or recurrent MI (i.e., among those patients who underwent nonurgent PCI), there was no difference in the timing of the PCI (125.5 h for ENOX [n = 1,885] vs. 120.3 h for UFH [n = 1,829]; p = 0.31). Among patients in whom recurrent ischemia or recurrent MI preceded the PCI (urgent PCI), the recurrent ischemia or MI and the ensuing PCI tended to occur later among patients treated with ENOX compared with UFH (79.2 h to PCI for ENOX [n = 278] vs. 67.1 h to PCI for UFH [n = 442]; p = 0.08). Once a recurrent MI occurred, the median time to PCI did not differ between ENOX and UFH (2.2 h vs. 2.6 h, respectively; p = 0.19). Therefore, the overall 12-h delay in the performance of PCI among ENOX patients relative to UFH patients was attributable primarily to a delay in the occurrence of recurrent ischemia/MI that triggered a PCI among ENOX patients.

**PRIMARY EFFICACY COMPARISON OF ENOX VERSUS UFH.** Among patients treated with PCI, the rates of the primary efficacy end point of death or nonfatal MI by 30 days were lower in the ENOX group than in the UFH group (10.7% of the ENOX vs. 13.8% of the UFH patients, 0.77 relative risk, 95% CI 0.66 to 0.90; p = 0.001) (Fig. 3, Table 4). This difference emerged before PCI and then persisted for up to 30 days. The reduction in death or nonfatal MI associated with ENOX administration remained statistically significant after adjustment for age, earlier aspirin use, time to PCI, smoking, time from symptom onset to fibrinolytic agent, type of fibrinolytic agent used (fibrin-specific or streptokinase), and the propensity to undergo PCI ($OR_{adj}$ 0.72, 95% CI 0.60 to 0.87; p = 0.001). The association of ENOX with a reduction in death or MI among patients undergoing PCI was also consistent across a wide range of key subgroups (Fig. 4). Enoxaparin administration was associated with a significantly lower incidence of death or MI even among those patients treated with glycoprotein IIb/IIIa inhibition (Fig. 4). Mortality did not differ by treatment group (2.9% for ENOX vs. 3.0% for UFH; p = 0.922).

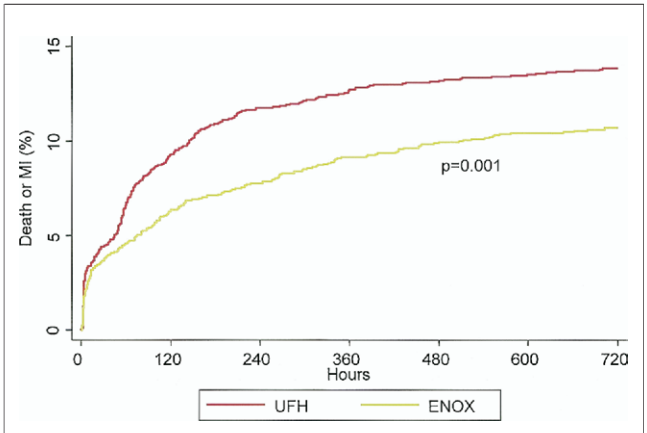


**Figure 3** **KM Failure for 30-Day Death or Recurrent MI by Randomization Group in the PCI Cohort**

Death or recurrent MI occurred less frequently in the ENOX group compared with the UFH group in the PCI cohort (p = 0.001 by log rank). KM = Kaplan-Meier; MI = myocardial infarction; other abbreviations as in Figure 1.

**Table 4** Efficacy, Safety, and Net Clinical Benefit Outcomes by Treatment Group Among Patients Undergoing PCI by 30 Days

| | ENOX (n = 2,272) | UFH (n = 2,404) | Relative Risk (95% CI) | p Value |
|---|---|---|---|---|
| Pre-PCI events, % (n) | | | | |
| MI | 5.9 (133) | 9.3 (223) | 0.63 (0.51–0.78) | <0.001 |
| Stroke | 0.04 (1) | 0.3 (7) | 0.15 (0.02–1.23) | 0.071 |
| Post-PCI events, % (n) | | | | |
| Death | 2.9 (66) | 3.0 (71) | 0.98 (0.71–1.37) | 0.922 |
| MI | 2.3 (53) | 2.2 (53) | 1.06 (0.73–1.54) | 0.763 |
| Stroke | 0.2 (5) | 0.6 (14) | 0.38 (0.14–1.05) | 0.052 |
| All events through 30 days, % (n) | | | | |
| Death | 2.9 (66) | 3.0 (71) | 0.98 (0.71–1.37) | 0.922 |
| MI | 8.2 (187) | 11.3 (272) | 0.73 (0.61–0.87) | <0.001 |
| Stroke | 0.3 (6) | 0.9 (21) | 0.30 (0.12–0.75) | 0.006 |
| TIMI major bleeding | 1.4 (32) | 1.6 (39) | 0.87 (0.55–1.39) | 0.561 |
| TIMI major bleeding and died by 30 days | 0.3 (7) | 0.4 (10) | 0.74 (0.28–1.95) | 0.545 |
| Intracranial hemorrhage | 0.2 (4) | 0.4 (10) | 0.42 (0.13–1.35) | 0.182 |
| TIMI minor bleeding | 3.3 (73) | 2.4 (58) | 1.34 (0.95–1.88) | 0.093 |
| TIMI major or minor bleeding | 4.6 (103) | 4.0 (95) | 1.15 (0.88–1.51) | 0.310 |
| Death/nonfatal MI | 10.7 (243) | 13.8 (332) | 0.77 (0.66–0.90) | 0.001 |
| Death/nonfatal MI/nonfatal major bleeding | 11.5 (261) | 14.8 (355) | 0.78 (0.67–0.90) | <0.001 |

Abbreviations as in Tables 1 and 2.

**INCIDENCE AND RELATIVE TIMING OF RECURRENT MI.** Enoxaparin administration was associated with a lower incidence of nonfatal recurrent MI among patients undergoing PCI (7.8% vs. 10.9%, $OR_{adj}$ 0.69, 95% CI 0.56 to 0.85; $p < 0.001$). In addition to a reduction in the incidence of recurrent MI in the ENOX group, the median time from randomization to recurrent MI was 37 h longer with ENOX (95.8 vs. 58.3 h; $p = 0.04$). Enoxaparin administration was associated with a reduction in recurrent MI before PCI (Table 4).

**PCI PERFORMED DURING ACTIVE TREATMENT WITH BLINDED STUDY DRUG.** In 2,178 patients, PCI was carried out while patients were receiving blinded study drug. The rate of PCI performed on blinded study drug did not differ between patients treated with ENOX and those with UFH (11.3% [1,103 of 9,788] vs. 11.0% [1,075 of 9,783]; $p = 0.53$). There was no difference in the time to PCI by treatment group during the phase when patients were treated with blinded study drug (medians 63.6 h for ENOX vs. 58.7 h for UFH; $p = 0.45$). Among patients undergoing PCI on blinded study drug, death or MI occurred less frequently in the ENOX group (13.0% vs. 16.7%, relative risk [RR] 0.77; $p = 0.013$). The reduction in death or nonfatal MI associated with ENOX administration remained statistically significant after adjustment for age, earlier aspirin use, duration of antithrombin therapy before PCI, smoking, time from symptom onset to fibrinolytic agent, type of fibrinolytic agent used (fibrin-specific or streptokinase), and the propensity to undergo PCI ($OR_{adj}$ 0.68, 95% CI 0.53 to 0.87; $p = 0.002$). There was no difference in major bleeding (1.8% with ENOX vs. 2.4% with UFH, RR 0.75; $p = 0.33$).

Among the cohort of patients who had blinded study drug discontinued before PCI and then resumed at the time of PCI (1.7% for ENOX and 5.2% for UFH; $p < 0.001$), death or MI occurred less frequently in the ENOX group than in the UFH group (5.9% vs. 14.4%, RR 0.41; $p = 0.004$). Among the cohort of patients whose blinded study drug was not discontinued before PCI (9.6% for ENOX and 5.8% for UFH; $p < 0.001$), death or MI occurred in 14.2% of the ENOX group compared with 18.9% of the UFH group (RR 0.75; $p = 0.018$).

**Safety end points.** Among the 4,676 patients undergoing PCI within 30 days, the rates of TIMI major bleeding were 1.4% in the ENOX group and 1.6% in the UFH group (RR 0.87; $p = 0.56$) (Table 4). There were also fewer strokes by 30 days in the ENOX group than in the UFH group (0.3% vs. 0.9%, RR 0.30; $p = 0.006$), a finding that was evident both before and after the PCI (Table 4). The rates of intracranial hemorrhage were similar by treatment group ($p = 0.18$). There were no differences in the rates of fatal bleeding, minor bleeding, and the composite of major or minor bleeding between the ENOX and UFH groups (Table 4). Likewise, in the cohort of patients who underwent PCI while on treatment with blinded study drug, there was no difference in the rate of bleeding (Table 5).

**NET CLINICAL BENEFIT.** The net clinical benefit composite end point of death, MI, or major bleeding was significantly lower at 30 days in the ENOX group (Table 4), a reduction in the absolute event rate of 3.3 absolute percentage points and an RR of 0.78 ($p < 0.001$). In the patients who underwent PCI while on treatment with blinded study drug, the net clinical end point was also lower by 4.3 absolute percentage points in the ENOX group (Table 5).

## Discussion

Among STEMI patients who undergo PCI after fibrinolytic agent administration, a strategy of ENOX administration for the duration of the index hospitalization was

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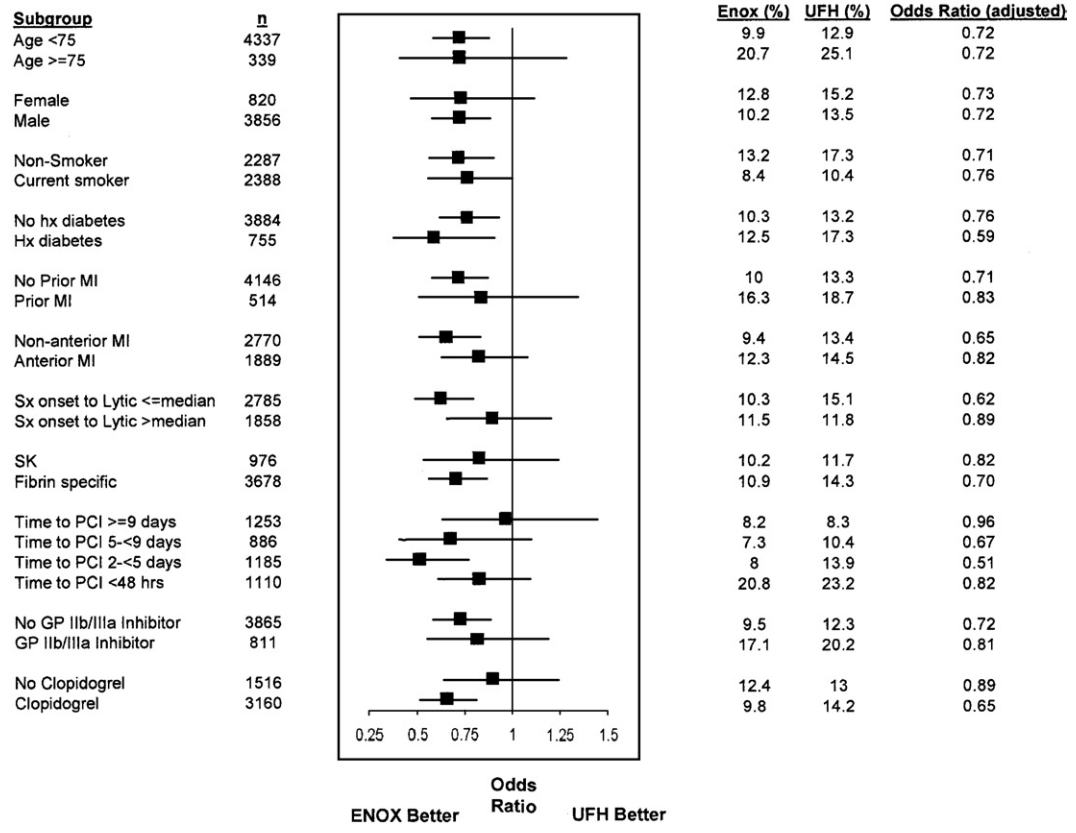


**Figure 4** Risk of 30-Day Death or Nonfatal Recurrent MI by Randomization Group According to Subgroups Among Patients Who Underwent PCI

GP = glycoprotein; Hx = history; SK = streptokinase; Sx = symptom; other abbreviations as in Figures 1 and 3.

superior to one of UFH for 48 h as adjunctive antithrombin therapy for the composite of efficacy and safety. One question that arises is whether the efficacy of the ENOX strategy was superior owing to its superiority as an antithrombin or whether it was owing to a longer duration of ENOX infusion. In the cohort of patients undergoing PCI during the blinded study drug phase, when both ENOX and UFH had been administered for a similar duration (63.6 h for ENOX vs. 58.7 h for UFH; p = 0.45), the efficacy of ENOX as an antithrombin was superior to UFH (death/MI 14.2% vs. 18.9%, $OR_{adj}$ 0.68; p = 0.002) without any increase in fatal or nonfatal bleeding. Finally, the superiority of ENOX was observed both among patients in whom study drug was administered continuously up to and through the performance of PCI as well as in patients in whom study drug was discontinued and then resumed for the performance of PCI. Thus, the superiority of ENOX was explained at least in part by superior antithrombin efficacy rather than simply a longer duration of therapy or due to rebound associated with UFH discontinuation.

**Table 5** Outcomes by Treatment Group Among Patients Who Underwent PCI While on Treatment With Blinded Study Drug

| | ENOX (n = 1,103) | UFH (n = 1,075) | Relative Risk (95% CI) | p Value |
|---|---|---|---|---|
| Individual end points | | | | |
| Death | 3.8% (42) | 4.0% (43) | 0.95 (0.63–1.44) | 0.817 |
| MI | 9.7% (107) | 13.3% (143) | 0.73 (0.58–0.92) | 0.008 |
| Stroke | 0.4% (4) | 0.8% (9) | 0.43 (0.13–1.40) | 0.173 |
| TIMI major bleeding | 1.8% (20) | 2.4% (26) | 0.75 (0.42–1.34) | 0.328 |
| TIMI minor bleeding | 3.7% (41) | 3.6% (39) | 1.03 (0.67–1.58) | 0.909 |
| Composite end points | | | | |
| Death/nonfatal MI | 13.0% (143) | 16.7% (180) | 0.77 (0.63–0.95) | 0.013 |
| Death/nonfatal MI/nonfatal major bleeding | 14.0% (154) | 18.3% (197) | 0.76 (0.63–0.92) | 0.006 |

Abbreviations as in Tables 1 and 2.

Enoxaparin administration was also associated with a reduced need for PCI (both during the blinded study drug administration phase and throughout 30 days) and likewise with deferred performance of PCI. The timing of nonurgent (i.e., elective) PCI did not differ between the UFH and ENOX arms, but urgent ischemia/recurrent MI that necessitated PCI tended to occur later and PCI was therefore performed later among patients treated with ENOX. This delay in the occurrence of ischemia-driven PCI may be especially beneficial in those patients who require interhospital transfer as part of their management for STEMI.

Finally, the risk of stroke is often cited as a barrier to performance of PCI after fibrinolytic agent administration. It is notable that ENOX administration was associated with a significantly lower incidence of stroke in patients undergoing PCI, which adds to the favorable net clinical benefit observed with ENOX.

The favorable efficacy observed with ENOX may be explained by the agent's superior antithrombin activity, which has been attributed to its greater anti-Xa:IIa ratio (9–11). It may also be explained by the rebound in thrombotic events following discontinuation of UFH. The favorable bleeding rates reported here may be explained at least in part by the fact that few patients were switched between antithrombins from pre- to post-randomization. Additionally, few patients crossed over from ENOX to UFH during the PCI, with a large portion of patients remaining on blinded study drug at the time of PCI. It has been speculated that both "switching" from pre-randomization assignment and "crossover" post-randomization accounted in part for the excess bleeding observed among patients treated with ENOX in SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors) (12), although a recent study by Cohen et al. (13) did not demonstrate an increase in bleeding with switching. The results of the present PCI cohort are similar to other recent studies showing comparable bleeding rates with ENOX and UFH in PCI (14,15).

Administration of ENOX also provided a seamless transition to the cardiac catheterization laboratory without the need for an additional antithrombin. The strategy of ENOX alone as antithrombin monotherapy contrasts with the strategies used in the OASIS (Organization to Assess Strategies for Ischemic Syndromes)-5 and -6 trials, in which UFH was administered in addition to ENOX or fondaparinux among patients undergoing PCI (16,17). In the present analysis, there was no excess bleeding (fatal or nonfatal) associated with ENOX compared with UFH as the sole adjunctive antithrombin strategy. Despite the fact that the rate of bleeding was numerically lower for ENOX, given the infrequent nature of bleeding events the statistical power of such a comparison is limited.

**Study limitations.** This is an analysis of a subgroup of patients in a randomized trial, and as such it is possible that both identified and unidentified confounders may have influenced the outcomes. The decision to perform PCI was at the discretion of the investigator. The ExTRACT-TIMI 25 trial was a comparison of a strategy of ENOX given through the index hospitalization compared with UFH given for at least 48 hours. Therefore, differences in outcomes between the 2 strategies may reflect differences in the type of anticoagulant as well as the duration of treatment. However, in the analysis of patients who underwent PCI while on blinded study drug, despite no difference in the duration of therapy (median 63.6 h for ENOX vs. 58.7 h for UFH; $p = 0.45$), ENOX was associated with a reduction in death or MI through 30 days compared with UFH. Strict enrollment criteria are used in clinical trials, and the results observed here may not be applicable to all patients in clinical practice. The pre-PCI patency status of the vessel was not recorded, so it could not be determined whether an occluded artery was being opened ("rescue PCI"), or whether an open artery was dilated ("adjunctive PCI").

**Clinical implications.** Compared with UFH, ENOX administration as an adjunct to fibrinolytic agent administration was associated with significantly fewer pre-PCI MIs as well as fewer strokes among patients with STEMI. Administration of ENOX provided a seamless transition to the cardiac catheterization laboratory without the need for an additional antithrombin. Adjunctive ENOX as administered in this study is preferred to UFH as the adjunctive antithrombin regimen to support a practice pattern in which PCI is performed at some time after fibrinolytic agent administration. Enoxaparin was associated with both delayed onset and reduced recurrence of MI, and both of these benefits may expand the window of opportunity to perform PCI after fibrinolytic agent administration.

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